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Research Progress of Anxiety and Depression Related to Chronic Fatigue Syndrome

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【**Abstract**】 The relationship between fatigue and diseases continues to receive widespread attention and fatigue is becoming an important public health issue. The World Health Organization added overexertion to the International Classification of Diseases in May, 2019, which had took effect globally in 2022. The concept of chronic fatigue syndrome （CFS） was proposed earlier, while its etiology and pathogenesis still remain unclear till now, resulting in lacking of specific therapies, which may be due to the involvement of multiple systems and the difficulties in distinguishing CFS symptoms from anxiety/depression, the complexity of the diagnosis and treatment of the disease and researches on it are also increased. This review initially investigates the characteristics of CFS associated with anxiety/depression, further explores the similarities and differences in indicator change characteristics between CFS and anxiety/depression in terms of the current research status on biological indicators, imaging abnormalities and treatment, in order to provide new ideas for the diagnosis and typing of CFS, and provide suggestions for conducting clinical and basic researches on the disease.

【**Key words**】 Fatigue syndrome, chronic；Anxiety；Depression；Neuroendocrine system；Immunity；Inflammation；Oxidative stress；Brain function；Review

Chronic fatigue syndrome （CFS）, also known as myalgic encephalomyelitis （ME）, is a debilitating condition characterized by persistent or recurrent fatigue. In addition to fatigue, it is often associated with symptoms such as pain, sleep disturbances, anxiety, and depression. The underlying mechanisms of CFS may involve immune dysregulation, neuroendocrine abnormalities, and disruptions in energy metabolism. Genetic studies have suggested that epigenetic modifications, including microRNA regulation, DNA methylation, protein phosphorylation, and histone modifications, may play a role in the development of CFS[1]. The incidence of CFS varies widely among different countries, genders, occupations, and age groups[2]. One contributing factor to this variability may be the lack of recognized objective biomarkers for the disease. Currently, CFS is primarily diagnosed based on clinical

symptoms, making it challenging to establish a definitive diagnosis. Stress is widely recognized as a major factor contributing to the onset and progression of CFS. Some researchers, like Xue Qi-lian et al[3], have classified CFS as a type of chronic stress-induced cortico-mesencephalic syndrome, a concept proposed by Soviet scholars. Although research in this area is relatively limited in China[4], the prevailing view is that social stress is closely linked to the development of CFS. Numerous studies conducted in the 21st century have shown that CFS often coincides with the occurrence of adverse life events, such as unemployment, divorce, accidents, or prolonged periods of depression or anxiety[2]. In 2004, a study in the United States found a significant increase in the incidence of CFS following the "September 11" terrorist attacks, suggesting a strong association between high-stress events and CFS development. Researchers like CHI et al[5] have even utilized stress-inducing methods like restraint, noise exposure, and crowding to create rat models of CFS. These models demonstrated fatigue-related changes in blood biochemical markers, mirroring trends observed in humans. However, it is important to note that these models do not fully capture the multifaceted pathogenesis seen in CFS patients[6]. Psychosocial factors are also considered significant contributors to CFS, and the condition can lead to varying degrees of psychosocial deficits and cognitive impairments[4]. The connection between CFS and comorbid anxiety and depression is a topic of particular importance and requires further investigation. Given these considerations, this article aims to explore the relationship between CFS and symptoms of anxiety and depression, drawing from existing research on CFS, biological alterations, imaging characteristics, and treatment modalities.

1 Literature Search Strategy

We conducted a comprehensive search of the PubMed, Web of Science, and CNKI databases from inception to February 2023. The Chinese search terms included "chronic fatigue syndrome" "depression" "anxiety" "neuroendocrine system" "immunity" "inflammation" "neuroimaging" "neurological system" "Neuroendocrine system neuroimaging" "oxidative stress" "brain function" and "chronic fatigue syndrome" "anxiety" "depression". Inclusion criteria encompassed literature related to the characteristics of CFS in relation to anxiety and depression, the current status of research on biological indicators, imaging abnormalities, and treatment. Exclusion criteria included literature unrelated to the article's topic, low-quality studies, and unavailability of full-text articles. In total, 61 articles were included.

2 Current Status of Research on CFS and Anxiety and Depression

Cella et al[7] discovered that nearly half of CFS patients exhibited at least one mood disorder, with these patients experiencing persistent and highly disabling symptoms during follow-up. Chen Ruohong et al[8] observed that fatigue

in CFS patients extended beyond physical aspects, manifesting as anxiety, depression, irritability, and emotional instability. However, Cockshell et al[9] found that fatigue in CFS patients did not appear to be closely associated with depressed mood. Studies investigating the correlation between CFS and mental health models revealed significant deficits in specific dimensions among CFS patients, which may directly contribute to the development of accompanying mood disorder symptoms[10]. As research on CFS deepens, investigations into CFS and mental health modeling have been spurred. Wright et al[11] concluded that maladaptive perfectionism is clearly linked to depressive symptoms in CFS patients, although no clear correlation with anxiety has been established. Sáez-Francàs et al[12] determined that depressive symptoms and hyperactivity can predict fatigue in CFS patients, while Daniels et al[13] identified anxiety as a significant contributor to fatigue in CFS patients.

The epidemiology of CFS is currently characterized by a higher prevalence among young and middle-aged women[14-15], often accompanied by significant anxiety and depression[16], resembling the epidemiology of depression. In studies involving children and adolescents with CFS and comorbid anxiety and depression, more attention has been directed toward exploring the role of family functioning. Bould et al[17] found that children or adolescents with CFS and comorbid depression were more likely to experience dysfunction and anxiety, indicating more complex and severe symptoms. Loade et al[18] discovered that depressed parents, particularly fathers, of children with CFS contributed to poor family functioning. The team also reported that the prevalence of comorbidity between CFS and anxiety and depression in adolescents was at least 30%, with varying rates depending on different questionnaires and scales. Furthermore, the proportion of adolescents with CFS experiencing suicidal tendencies exceeded that of adults with major depression and anxiety, highlighting the importance of routine assessment for anxiety and depression in adolescents with CFS[19]. In conclusion, there appears to be a close relationship between CFS and the severity of anxiety and depression symptoms, warranting further in-depth investigation.

3 Biological Changes Associated with Anxiety and Depression in CFS

3.1 Oxidative Stress and Metabolism Patients with CFS may exhibit metabolic changes related to oxidative stress in the brain. Kennedy et al[20] observed significantly elevated plasma oxidative stress markers （F2 isopropanes）in CFS patients compared to healthy individuals, with a certain correlation between the trend of these changes and symptom variation. Shungu et al[21] found that cerebrospinal fluid lactate levels were significantly higher in CFS patients, indicating abnormalities in oxidative stress and energy metabolism. However, this indicator displayed a similar elevation in patients with major depressive disorder, making it suggestive of comorbidities rather than a differentiating biomarker between the two disorders. Notably, the elevation of this indicator was more pronounced in

CFS patients than in individuals with generalized anxiety disorder, suggesting its potential value in differentiation[21]. Additionally, CFS patients displayed significantly increased tryptophan concentration in blood indices, suggesting amino acid metabolism abnormalities in these patients. Animal studies have also revealed that chronic stress can lead to the gradual accumulation of glutamate in the brain, resulting in neuronal apoptosis and subsequent emotional, cognitive, and hypothalamic-endocrine dysfunctions. These findings suggest that CFS is not purely a "psychological or psychiatric" disorder, as it has a biological basis rooted in metabolic abnormalities. Fatigue, anxiety, and depression may be symptoms associated with brain metabolic abnormalities.

3.2 Immune, Inflammatory, and Endocrine Related Attree et al[22] noted that while the pathophysiological mechanisms of CFS remain unclear, clear abnormalities in the immune system are evident, and fatigue and depression may be the result or consequence of neurobiological changes in CFS. Lorusso et al[23] suggested that intrinsic immune abnormalities associated with CFS involve the overactivation of pro-inflammatory factors, lymphoid subsets, and a reduction in immune responses driven by helper T-cells （Th1）. Groven et al[24] observed a tendency for plasma tumor necrosis factor-alpha （TNF-α） levels to increase in CFS patients compared to healthy controls, with a correlation between elevated interleukin （IL）-10 levels and the severity of physical symptoms. Studying changes in the types or quantities of cytokines in plasma or cerebrospinal fluid can further clarify the potential pathogenic mechanisms of CFS and lead to effective treatments. CFS patients are characterized by mild hypocortisolism and a diminished circadian rhythm of cortisol[25]. Torres-Harding et al[26] demonstrated a reduction in salivary cortisol in fatigue patients within 24 hours. Moreover, a correlation was found between elevated levels of interleukin （IL-10） and the severity of physical symptoms. In a subsequent trial, Herane-Vives et al[27] discovered similarities between patients with depression and CFS, with both disorders exhibiting reduced salivary cortisol but normal cumulative hair cortisol levels. This suggests that certain subtypes of depression and CFS may warrant further investigation into comorbidity studies. Many studies have reported downregulation of the hypothalamic-pituitary-adrenal （HPA） axis activity in patients with CFS, as well as in those with anxiety and depression. This phenomenon may be related to the alteration of certain cytokines （e.g., IL-1, IL-6）, although the overall mechanism remains unclear[28-31].

3.3 Biopathogenesis Various factors, including bacteria, viruses, and eukaryotes, influence the onset and progression of CFS through host-associated effects[32]. Initially, CFS was linked to Epstein-Barr virus （EBV） infection, but subsequent research found that infections with human herpesvirus （HHV） type 6 and cytomegalovirus could also induce CFS[33]. Chinese scholars have reported a higher probability of active HHV and EBV infections in the CFS population[34]. Microvirus infections have also been identified in CFS individuals[35].

CFS patients frequently exhibit gastrointestinal dysfunction, suggesting a potential relationship between dysbiosis of the intestinal flora and the onset and persistence of CFS symptoms. Giloteaux et al[36] discovered significantly reduced bacterial diversity, particularly in members of the phylum Firmicutes, in specimens from CFS patients using high-throughput sequencing technology. Recent studies on the intestinal flora of patients with anxiety and depression have revealed reduced abundance of specific bacterial groups in these patient populations[37]. Moreover, related research has indicated a mutually reinforcing process between anxiety, depression, and pathogenic microbial infections. The causal relationship between these factors warrants further exploration. The connection between CFS, concomitant anxiety and depression symptoms, and biopathogenesis, along with related mechanisms, necessitates further stratification and study.

4 Imaging and Electrophysiological Characteristics of CFS in Patients with Anxiety and Depression

4.1 Imaging Characteristics While CFS is primarily considered a neurological disorder, its complex features overlap with various systemic disorders like irritable bowel syndrome, hyperventilation syndrome, and rheumatic polymyalgia[38]. Understanding the mechanism of abnormal brain function in CFS is crucial to addressing these overlapping questions. The relationship between anxiety, depression, and abnormal brain function has gradually become evident with advancements in neuroimaging technology[39-40].

Presently, advanced imaging techniques such as functional magnetic resonance imaging （fMRI）, single-photon emission computed tomography （SPECT）, and positron emission tomography （PET） are employed to analyze brain activity in CFS patients[41]. Magnetic resonance spectroscopy （MRS） analysis revealed that the choline/creatine ratio in the occipital cortex of CFS patients was significantly higher than that of healthy subjects[42-43]. Feng Chuwen et al[44] summarized that CFS patients exhibit distinctive MRI features related to brain morphology, cerebral blood flow, cerebral functional connectivity, and cerebral metabolism. Numerous imaging studies have confirmed reduced cortical blood flow, abnormal gray matter and white matter signals, among other anomalies, in CFS patients. BARNDEN et al[45] reported increased myelin formation in the prefrontal lobe, reduced white matter volume in the midbrain, and neuroinflammation in CFS patients. However, reduced white matter volume has also been found in patients with depression. PURI et al[46] identified reduced gray matter volumes （GMV） in specific brain regions of CFS patients, while Jia Yanbin et al[47] reported reduced gray matter volumes in the same areas in patients with depression. These imaging characteristics, shared between CFS and anxiety and depression, indicate both similarities and differences between the conditions. Further research is needed to explore the relationship between these characteristics and the underlying disease mechanisms and symptoms. In recent years, multimodal

MRI technology has been used to analyze the correlation between symptoms and changes in brain function. It provides a systematic evaluation of the effects of medications, cognitive therapy, physical therapy, and other treatments. Due to its convenience, non-invasiveness, acceptability, and standardization, neuroimaging technology is likely to become a major tool in functional neurological disease research, clinical diagnosis, and treatment assessment. Studies involving CFS patients with symptoms of anxiety and depression should consider these indexes as key indicators for content assessment.

4.2 Characteristics of Brain Electrophysiology In contrast to neuroimaging techniques, neurophysiology, particularly electroencephalography （EEG）, offers high temporal resolution. EEG records the electrophysiological activity of brain nerve cells. CFS patients exhibit reduced δ, θ, and α amplitudes in the frontal limbic region, and altered EEG activity may be a distinctive feature of CFS[48-49]. Event-related potentials （ERPs） are a specialized form of EEG that reflects the changes in cortical neurophysiology during cognitive processes[50-51]. CFS patients display alterations in N1, N2, P2, and P3 components. Liu Zhengkang[52] found that CFS patients with depression showed higher N2 amplitude and longer P3 latency during visual stimulation with international mood pictures compared to healthy subjects. Excessive enhancements in cognitive processing of mood pictures, perception, attention, automatic active processing, and depth processing activities of negative pictures in CFS patients may be related to their long-term negative emotional state. These electrophysiological findings, shared between CFS and depression, highlight the significance of studying their underlying mechanisms and the potential role of neurophysiology in characterizing these conditions.

5 Treatment of CFS and Comorbid Anxiety and Depression

Among non-pharmacological therapies, two effective treatments for CFS are cognitive-behavioral therapy （CBT） and graded exercise therapy[53-54]. Some scholars have also proposed homeopathy and multivitamin therapy[55-56]. However, drug therapy remains more convenient in clinical practice and can provide noticeable short-term relief[57]. The effectiveness of antiviral drugs, hormones, and immunomodulators for CFS patients is still inconclusive, with some patients experiencing worsened symptoms after use. Conversely, antidepressants are more effective for most patients and can significantly improve their symptoms. The author believes that the differences in treatment efficacy mentioned above can be attributed, in part, to diagnostic criteria, leading to heterogeneity among research subjects. By establishing objective diagnostic indicators for inclusion criteria or by separating the study of CFS with or without symptoms of anxiety and depression, we may expect to significantly reduce differences in treatment effects. Attempts can also be made to determine the comorbid relationship between CFS and anxiety and

depression using scales or other examination methods, thus further elucidating the effects of anxiolytic and antidepressant drugs in alleviating fatigue. DANIELS et al[58] emphasized in their 2019 study the importance of routinely investigating comorbid anxiety and depression in CFS. They noted that the depressive and anxiety states of CFS patients are clearly associated with adverse treatment outcomes in CBT. Therefore, a better understanding of the intrinsic mechanisms linking CFS, anxiety, and depression is essential to tailor treatments more effectively, ultimately benefiting a larger number of CFS patients.

6 Summary

The incidence of CFS in China has significantly increased due to rising social pressures, environmental factors, infectious diseases, and other influences[59]. The persistent, unrelenting symptoms of CFS severely impact patients' daily lives and work. Despite meaningful explorations in this field both domestically and internationally[60-61], the diagnosis and treatment of CFS can only be improved in the future through innovative studies that focus on objective indices for CFS diagnosis and prognosis assessment. Due to the heterogeneous nature of CFS and its substantial overlap with anxiety and depression, further research should explore CFS through functional neuroimaging, genetics, and inflammatory immunology. It should consider CFS symptom characteristics, severity, and fluctuation patterns. This research aims to clarify the causal relationship between symptoms such as fatigue, anxiety, and depression and changes in brain function. Achieving this will hold significant practical importance in understanding the pathogenesis of CFS, enhancing physicians' knowledge of the disease, and exploring reliable and effective treatment methods.

Authors' contributions: Liu Xinyi was responsible for the conception and design of the article, the collection and organization of research data, and the writing of the paper; Liu Zhandong was responsible for the revision of the paper, quality control and proofreading of the article, and was responsible for the overall management and supervision of the article.

There is no conflict of interest in this article.

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